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(71) Applicants:
- **Senju Pharmaceutical Co., Ltd.**
  Osaka-shi, Osaka 541-0046 (JP)
- **Kyorin Pharmaceutical Co., Ltd.**
  Tokyo 101-8311 (JP)

(72) Inventors:
- **YASUEDA, Shinjchi**
  Kobe-shi, Hyogo 655-0021 (JP)
- **INADA, Katsuhiro**
  Kobe-shi, Hyogo 651-2242 (JP)

(74) Representative: **Hall, Marina**
Elkington and Fife
Prospect House,
8 Pembroke Road
Sevenoaks, Kent TN13 1XR (GB)

(54) AQUEOUS LIQUID PREPARATIONS

(57) Aqueous liquid preparations containing gatifloxacin (chemical name: (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-quinolinecarboxylic acid) or its salt and sodium edetate; and a method for enhancing the corneal permeability of gatifloxacin, a method for preventing crystallization of gatifloxacin and a method for preventing coloration of gatifloxacin each by blending gatifloxacin or its salt with sodium edetate.

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Descripti n

FIELD OF THE INVENTION

[0001] The present invention relates to an aqueous liquid pharmaceutical composition comprising as a main component a quinolone carboxylic acid derivative, Gatifloxacin (chemical nomenclature: (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid). Further, the present invention relates to a method for raising corneal permeability of Gatifloxacin, a method for preventing precipitation of Gatifloxacin crystals, and a method for preventing coloration of Gatifloxacin.

BACKGROUND OF THE INVENTION

[0002] Gatifloxacin is a new quinolone antimicrobial agent which is recognized to exhibit a strong antimicrobial activity against not only Gram-negative bacteria but also Gram-positive bacteria, anaerobes and mycoplasmas. Then, it has been proposed to apply it to ophthalmological infectious diseases such as conjunctivitis, dacryocystitis, hordeolum etc. and otorhinological infectious diseases such as otitis externa, otitis media, sinusitis etc (see JP-B 8-9597).

[0003] For designing a pharmaceutical preparation in the form of eye drops containing an antimicrobial agent, an index is to raise corneal permeability of the agent to increase the amount of the agent to transfer to aqueous humor. However, in general, the agent applied to eyes can scarcely pass into inside of the eyes because of dilution with tears and the barrier function of corneas. Then, as a method of improving corneal permeability of the agent, a method using an absorption enhancer has been proposed. In addition, a method using a viscous base material has been proposed to increase the agent-retentivity at the anterior ocular segment.

OBJECTS OF THE INVENTION

[0004] With regard to Gatifloxacin, although its application to ophthalmological or otorhinological infectious diseases has been proposed, there is no report about a study of an aqueous liquid pharmaceutical composition thereof for topical administration, which can be actually applied to eyes, for example, its passing into inside of eyes, stability, etc.

[0005] In view of these circumstances, an object of the present invention is to permit actual application of Gatifloxacin in ophthalmological or otorhinological field, in particular, to provide an aqueous liquid pharmaceutical composition comprising as an effective component Gatifloxacin.

SUMMARY OF THE INVENTION

[0006] The present inventors have intensively studied to apply Gatifloxacin in ophthalmological field and, consequently, have found that this objective can be achieved by coexistence of Gatifloxacin with disodium edetate.

[0007] Disodium edetate is considered to lower the calcium concentration in corneal epithelium cells and expanding intercellular spaces, thereby accelerating passing of a water-soluble medicament into inside of eyes. However, a rise in corneal permeability of a medicament depends on a concentration of disodium edetate (Journal of Pharmaceutical Science, 77: 3-14, 1988) and, normally, at present, disodium edetate should be used at a high concentration as much as 0.5% (Investigative Ophthalmology & Visual Science, 26: 110-113, 1985; Experimental Eye Research, 54: 747-757, 1992; Pharmaceutical Research, 12: 1146-1150). Nevertheless, the present inventors have found that corneal permeability of Gatifloxacin can be improved at a lower concentration of disodium edetate.

[0008] Further, it has been known that the solubility of Gatifloxacin depends on pH and its solubility at about physiological pH is very low. Then, in order to dissolve a sufficient amount of Gatifloxacin in an aqueous liquid pharmaceutical composition, pH of the composition should be adjusted to an acidic or alkaline range, which causes a problem such as irritation upon topical administration. However, the present inventors also have found that the solubility of Gatifloxacin at about physiological pH is improved by coexistence thereof with disodium edetate.

[0009] The present invention has been completed based on these present inventors' novel findings and, according to the present invention, there is provided an aqueous liquid pharmaceutical composition which comprises Gatifloxacin or its salt and disodium edetate. In particular, the aqueous liquid pharmaceutical composition of the present invention is an aqueous solution containing Gatifloxacin or its salt and disodium edetate.

[0010] Further, the present invention provides a method for raising corneal permeability of Gatifloxacin which comprises incorporating disodium edetate into eye drops containing Gatifloxacin or its salt; a method for preventing precipitation of Gatifloxacin crystals which comprises incorporating disodium edetate into an aqueous liquid preparation containing Gatifloxacin or its salt; and a method for preventing coloration of Gatifloxacin which comprises incorporating disodium edetate into an aqueous liquid preparation containing Gatifloxacin or its salt.

[0011] This object as well as other objects and advantages of the present invention will become apparent to those

skilled in the art from the following description.

DETAILED DESCRIPTION OF THE INVENTION

[0012] In the present invention, Gatifloxacin or its salt is used as the effective component. Examples of the salt of Gatifloxacin used in the present invention include those with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, etc.; those with organic acids such as methanesulfonic acid, lactic acid, oxalic acid, acetic acid, etc.; or those with sodium, potassium, magnesium, calcium, aluminum, cerium, chromium, cobalt, copper, iron, zinc, platinum, silver, etc.

[0013] Normally, the amount of Gatifloxacin or its salt (hereinafter sometimes simply referred to as "Gatifloxacin") to be formulated in the aqueous liquid pharmaceutical composition of the present invention is varied according to the degree of infection of a particular subject, but normally, Gatifloxacin is formulated within the range of 0.1 to 1.0 w/v%, preferably 0.1 to 0.8 w/v%, more preferably 0.3 to 0.5 w/v%.

[0014] Normally, disodium edetate is formulated in an amount of 0.001 to 0.2 w/v%, preferably 0.005 to 0.1 w/v%, more preferably 0.01 to 0.1 w/v%.

[0015] Normally, the aqueous liquid pharmaceutical composition of the present invention is adjusted to pH 5 to 8, preferably pH 5.5 to 7.5, more preferably pH 6 to 7.

[0016] If necessary, the aqueous liquid pharmaceutical composition of the present invention may further contain appropriate additives, for example, an isotonic agent (e.g., sodium chloride, potassium chloride, boric acid, glycerin, propylene glycol, mannitol, sorbitol, glucose etc.); a buffer solution (e.g., phosphate buffer solution, acetate butter solution, borate buffer solution, citrate buffer solution, glutamic acid, ε -aminocapronic acid, etc.); a preservative (e.g., benzalkonium chloride, benzethonium chloride, chlorhexidine gluconate, chlorobutanol, benzyl alcohol, sodium dehydroacetate, p-hydroxybenzoate, etc.), a thickening agent (e.g., methylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, sodium hyaluronate, carboxyvinyl polymer, polyvinyl alcohol, polyvinyl pyrrolidone, Macrogol (polyethylene glycol), etc.), a pH adjusting agent (e.g., hydrochloric acid, sodium hydroxide, acetic acid, phosphoric acid, etc.), and the like.

[0017] The aqueous liquid pharmaceutical composition of the present invention can be produced by a per se known method. For example, it can be produced by the process described in the section of "Ophthalmic Solutions" or "Liquids and Solutions", General Rules for Preparations, The Japanese Pharmacopoeia Thirteenth Edition.

[0018] The aqueous liquid pharmaceutical composition of the present invention has antimicrobial activity and can be used for prophylaxis and therapy of blepharitis, hordeolum, dacryocystitis, conjunctivitis, tarsitis, keratitis, corneal ulcer, postoperative infection, and the like. For this purpose, the composition can be instilled in the eye about three times a day at a dosage of one drop per once. For otitis externa or otitis media, normally, the composition can be instilled in the ear twice a day at a dosage of 6 to 10 drops per once. Further, for sinusitis, normally, the composition can be sprayed and inhaled three times every other day in a week at a dosage of 2 to 4 ml per once, or can be administered in the maxillary sinus once a week at a dosage of 1 ml per once. The dosage can be increased or decreased according to the degree of a particular disease condition.

[0019] The present invention will be further illustrated by the following experiments and examples, but the present invention is not limited thereto.

Experiment 1

Effect of disodium edetate on transfer of Gatifloxacin to aqueous humor

Method

[0020] According to the formulations of Table 1, eye drops of Gatifloxacin were prepared (formulations A-C). Each of the eye drops (50 µl/eye) was instilled once in the eyes of male Japanese albino rabbits (body weight: about 2 kg). At one hour after the instillation, the aqueous humor was collected and the Gatifloxacin concentration was determined by HPLC.

Table 1

Formulations	A	B	C
Gatifloxacin	0.5 g	0.5 g	0.5 g
Disodium edetate	-	-	0.05 g

Table 1 (continued)

Formulations	A	B	C
Sodium chloride	0.9 g	0.9 g	0.9 g
Hydrochloric acid	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.
Sterilized purified water	to total 100 ml	to total 100 ml	to total 100 ml
pH	7.0	6.0	6.0

Results

[0021] The concentration of Gatifloxacin in the aqueous humor at one hour after the instillation is shown in Table 2.

[0022] When pH dropped, the amount of Gatifloxacin transferred to the aqueous humor decreased. For the formulation adjusted to pH 6.0 (formulation C), the amount of Gatifloxacin transferred to the aqueous humor increased by about 1.2 times and 1.5 times as much as those of the formulations A (pH 7.0) and B (pH 6.0) which were used as controls, respectively.

[0023] Since the concentration of disodium edetate normally used for raising corneal permeability is 0.5 w/v%, these results show that corneal permeability of Gatifloxacin has been improved even by using disodium edetate in 1/10 amount as much as that normally used.

Table 2

Formulations	Gatifloxacin concentration in aqueous humor (μg/ml)
A	1.61 ± 0.43
B	1.30 ± 0.42
C	1.93 ± 0.95

Experiment 2

Effect of disodium edetate on precipitation of Gatifloxacin crystals

Method

[0024] According to the formulations of Table 3, aqueous liquid preparations of Gatifloxacin were prepared (formulations B-D). Each solution was filled in 5 ml glass ampoules. The ampoules were subjected to freezing at -30°C (overnight) and then thawing at room temperature repeatedly to observe precipitation of Gatifloxacin crystals.

Table 3

Formulations	B	C	D
Gatifloxacin	0.5 g	0.5 g	0.5 g
Disodium edetate	-	0.05 g	0.1 g
Sodium chloride	0.9 g	0.9 g	0.9 g
Hydrochloric acid	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.
Sterilized purified water	to total 100 ml	to total 100 ml	to total 100 ml
pH	6.0	6.0	6.0

Results

[0025] In the formulation in which disodium edetate was not formulated (formulation B), crystals were precipitated when freezing and thawing were repeated twice to three times. On the other hand, when disodium edetate was formulated (formulations C and D), no precipitation of crystals was recognized even when freezing and thawing were repeated ten times.

[0026] These results show that precipitation of Gatifloxacin crystals under storage conditions at a low temperature is prevented by formulating disodium edetate in an aqueous liquid preparation of Gatifloxacin.

Experiment 3

Effect of disodium edetate on preventing coloration of Gatifloxacin

Method

[0027] Sodium chloride (0.86 g) and 0.1 mol/liter hydrochloric acid (5.2 ml) were added to sterilized purified water (80 ml) in a stainless steel (SUS316) beaker of 8 cm diameter and the mixture was stirred. Then, Gatifloxacin (0.32 g) and disodium edetate (at a final concentration of 0%, 0.001%, 0.005%, 0.01% or 0.05%) were added thereto and dissolved therein. The solution was adjusted to pH 6.5 with 0.1 mol/liter sodium hydroxide and the total volume was made up to 100 ml to obtain an aqueous liquid preparation of Gatifloxacin. A color difference between the aqueous liquid preparation and sterilized purified water was determined with a differential colorimeter (Chroma meter CT-210C manufactured by Minolta, light source Lab table system). As a control, an aqueous liquid preparation of Gatifloxacin prepared in a glass beaker was used.

Results

[0028] The color difference determined is shown in Table 4.

[0029] The aqueous liquid preparation prepared in the glass beaker and used as the control had the color difference of 1.9 to 2.0 and a pale yellow color. On the other hand, the aqueous liquid preparation prepared in the stainless steel beaker had the color difference of 3.17 in case that disodium edetate was not added and 2.42 in case that 0.01% of disodium edetate was added. They had a light yellow color and a pale yellow color, respectively. Thus, they were discolored by formulating disodium edetate.

[0030] In view of these results, it is considered that Gatifloxacin is colored by the metal ion dissolved in the preparation from the stainless steel beaker. Further, these results show that addition of disodium edetate can prevent coloration of Gatifloxacin.

Table 4

Concentration of disodium edetate (%)	Color Difference	
	Stainless Steel Beaker	Glass Beaker
0	3.17	1.90
0.001	3.08	1.93
0.005	3.05	2.02
0.01	2.42	1.94
0.05	2.19	1.93

Example 1

[0031] According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.5 g
Disodium edetate	0.1 g
Sodium chloride	0.9 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	7.0

Example 2

[0032] According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.5 g
Disodium edetate	0.05 g
Sodium chloride	0.9 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
sterilized purified water	up to 100 ml
pH	7.0

Example 3

[0033] According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.5 g
Disodium edetate	0.1 g
Sodium dihydrogen phosphate	0.1 g
Sodium chloride	0.9 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	7.0

Example 4

[0034] According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.3 g
Disodium edetate	0.05 g
Sodium chloride	0.9 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	6.0

Example 5

[0035] According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.5 g
Sodium edetate	0.01 g
Glycerin	2.6 g
Benzalkonium chloride	0.005 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	7.5

Example 6

[0036] According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.5 g
Sodium edetate	0.05 g
Sodium chloride	0.9 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.

(continued)

Ingredients	Amount
Sterilized purified water	up to 100 ml
pH	5.5

Example 7

[0037] According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.3 g
Disodium edetate	0.05 g
Sodium chloride	0.9 g
Hydroxypropylmethyl cellulose	0.1 g
Methyl p-hydroxybenzoate	0.026 g
Propyl p-hydroxybenzoate	0.014 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	6.0

Example 8

[0038] According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.5 g
Disodium edetate	0.01 g
Sodium chloride	0.83 g
Benzalkonium chloride	0.005 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	5.5

Example 9

[0039] According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients	Amount
Gatifloxacin	0.3 g
Disodium edetate	0.01 g
Sodium chloride	0.86 g
Benzalkonium chloride	0.005 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Sterilized purified water	up to 100 ml
pH	6.0

[0040] As shown in Experiment 1, according to the eye drops of the present invention, corneal permeability of the effective component, Gatifloxacin, can be improved even by using disodium edetate in 1/10 amount as much as that normally used. Further, as shown in Experiment 2, the aqueous liquid preparation of the present invention can prevent precipitation of Gatifloxacin crystals under storage conditions as a low temperature. Furthermore, as shown in Experiment 3, coloration of Gatifloxacin by a metal ion can be prevented. Thus, the aqueous liquid preparation of the present invention is very useful.

Claims

1. An aqueous liquid pharmaceutical composition which comprises Gatifloxacin or its salt and disodium edetate.

2. The aqueous liquid pharmaceutical composition according to claim 1, wherein pH of the composition is within the range of 5 to 8.

3. The aqueous liquid pharmaceutical composition according to claim 1 or 2, where the composition is in the form of eye drops.

4. The aqueous liquid pharmaceutical composition according to claim 1 or 2, where the composition is in the form of ear drops.

5. The aqueous liquid pharmaceutical composition according to claim 1 or 2, where the composition is in the form of nasal drops.

6. A method for raising corneal permeability of Gatifloxacin which comprises incorporating disodium edetate into eye drops containing Gatifloxacin or its salt.

7. A method for preventing precipitation of Gatifloxacin crystals which comprises incorporating disodium edetate into an aqueous liquid preparation containing Gatifloxacin or its salt.

8. A method for preventing coloration of Gatifloxacin which comprises incorporating disodium edetate into an aqueous liquid preparation containing Gatifloxacin or its salt.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/04483

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] A61K31/495, 9/08, 47/18//C07D401/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] A61K31/495, 9/08, 47/18//C07D401/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, 62-252772, A (Kyorin Pharmaceutical Co., Ltd.), 4 November, 1987 (04. 11. 87), Claims ; page 9, lower left column, lines 8 to 13 & EP, 230295, A2 & US, 4980470, A & US, 5043450, A	1-8
Y	JP, 63-174930, A (Hokuriku Seiyaku Co., Ltd.), 19 July, 1988 (19. 07. 88), Claims ; page 2, upper left column, lines 19 to 22, upper right column, line 14 to lower left column, line 1 ; page 2, lower right column, 4th line from the bottom to page 3, lower left column & GB, 2199745, A & DE, 3715818, A & FR, 2609394, A & US, 4780465, A	1-8
Y	TANAKA, Masatoshi et al., Emergence of In Vitro Resistance to Fluoroquinolones in *Neisseria gonorrhoeae* Isolated in Japan, ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 1995, Vol. 39, No. 10, pp.2367-2370, Reference as a whole	1-8

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search	Date of mailing of the international search report
19 October, 1999 (19. 10. 99)	26 October, 1999 (26. 10. 99)
Name and mailing address of the ISA/ Japanese Pat nt Offic	Authorized officer
Facsimile No.	Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/04483

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KUBO Shuta et al., Enhanced Chemiluminescence Response of Polymorphonuclear Leukocytes by New Quinolone Antimicrobials, Chemotherapy, 1994, Vol. 40, No. 5, pp.333-336 Reference as a whole	1-8
Y	SASAKI, Hitoshi et al., Different Effects of Absorption Promoters on Corneal and Conjunctival Penetration of Ophthalmic Beta-Blockers, Pharmaceutical Research, 1995, Vol. 12, No. 8, pp.1146-1150, Reference as a whole	6

Form PCT/ISA/210 (continuation of second sheet) (July 1992)